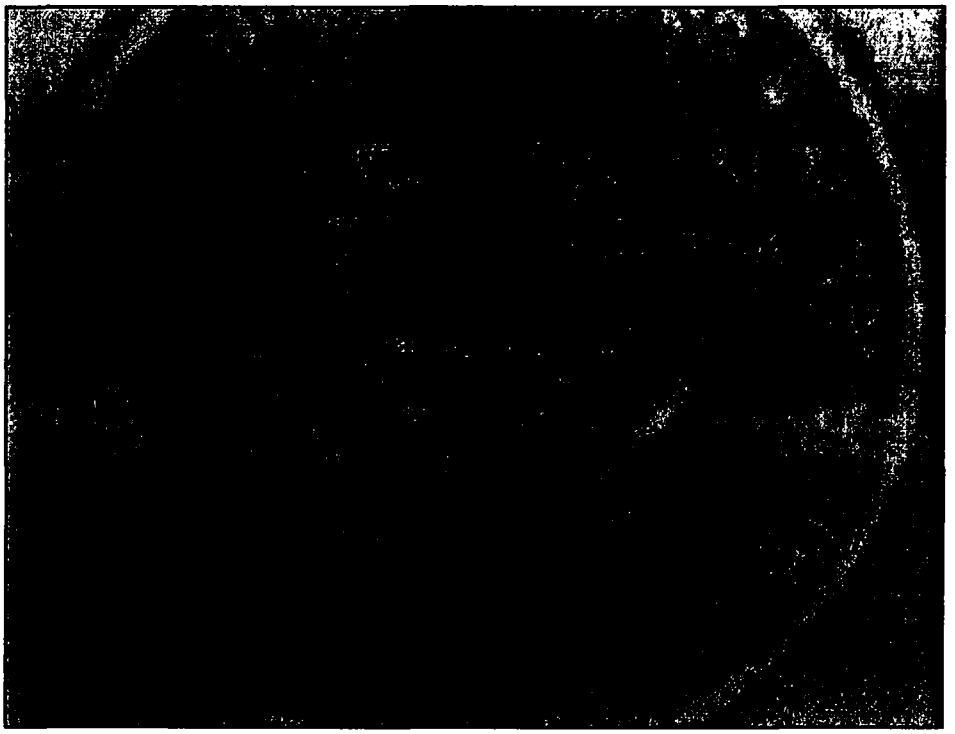

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Organization of Presentation

1. Status of IRIS Cancer Evaluation

2. Comments on a Libby Amphibole Toxicity Assessment

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IRIS Cancer Evaluation

- Formally announced and initiated in Feb 2006 Federal Register
- Planning Stages
- Proposed Phased Approach

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IRIS Cancer Evaluation Groundwork

- 2001, Asbestos Health Effects Conference, Oakland, CA
- 2003, Asbestos Mechanisms of Toxicity Workshop
- Collaboration with NIOSH for archived filter reanalysis
  - South Carolina Textile Plant (chrysotile)
  - NIOSH is publishing update
- Better characterization of historical asbestos exposure project
  - Comparison of exposures in key chrysotile and amphibole exposed cohorts
  - Project cancelled – data unavailability

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IRIS Cancer Evaluation

Purpose of the Phased Approach

- Address key technical issues, early in the project
- Provide technical building blocks for the cancer assessment
- Provide flexibility in document development as new data become available

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Proposed Phased Approach

- **Phase 1:** *Preparatory phase, laying the ground work*
- **Phase 2:** *Quantitative work and document development*
- **Finalization of document:** *Review and revision*

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Phase 1

- Scoping meeting (August 31, 2006)
  - Invited input from key individuals working on different asbestos issues across the Agency
- Develop literature summaries and issue papers
  - Address key controversial issues
  - Provide technical building blocks for development of cancer assessment
- Investigate studies to better understand dose-response
  - Identify occupational cohorts for better exposure characterization
  - Identify data availability for nonoccupational cohorts

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Libby Amphibole Toxicity Assessment

- Available epidemiologic data
- Data Gaps
- Possible objectives for animal studies

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Libby Amphibole

Available Epidemiologic Studies

- Libby Worker Mortality Studies
  - The Morbidity and Mortality of vermiculite miners and millers to tremolite-actinolite, (Amandus and Wheeler, 1987)
  - Cohort study of mortality of vermiculite miners exposed to tremolite (McDonald et al, 1986) (Updates in 2002 and 2004)
  - Vermiculite, Respiratory Disease and asbestos exposure in Libby Montanna: Update of a cohort mortality study (P. Sullivan, 2007)

Vermiculite miners: Enoree, SC

- Health of vermiculite minors exposed to trace amounts of vermiculite (McDonald et al, 1988)

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Libby Amphibole Toxicity Assessment

- Three analyses of the Libby worker cohort are available support lung cancer estimate, which provide consistent results
- Sullivan's paper indicates data may be available to support quantitative risk estimates for Mesothelioma

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Libby Amphibole Toxicity Assessment

- Exposure estimates
  - PCM counts of personal filters
  - Data collected by WR Grace
  - Data collection forms and filters may be available to EPA
- TEM surrogate metric is possible
  - Review of current and historical data indicate fiber size profile is fairly consistent
  - Convert historical PCM to TEM surrogate measure of material present

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Libby Amphibole Toxicity Assessment

- May be derived from human epidemiologic data for both lung cancer and mesothelioma
- Derivation could be based on the Libby amphibole
- EPA policy is to use human data where available and of appropriate quality

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Libby Amphibole Toxicity Assessment

Use of Libby cohort reduces technical and legal debates with respect to the Libby amphibole

- Fiber form
  (asbestiform, fiber, prismatic, cleavage fragment)
- Fiber mineralogy
- Influence of fiber dimension

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Libby Amphibole Toxicity Assessment Data Gaps

- Smoking status in Libby worker cohort
- Libby amphibole specific Mode of Action information
- Some uncertainty in exposure estimates
- Shape of low dose response curve
- Susceptibility for early-lifetime exposure

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Animal Studies: Improve Derivation of an Inhalation Unit Risk

- **Mode of Action**
  - Demonstrate fiber toxicity *in vitro/in vivo* (e.g. plausibility)
    - *Similar biological activity as other forms of asbestos*
    - Relative toxicity to other forms of asbestos
  - Examine role of various mechanisms to inform DR curve
    - ROS/RNS
    - Direct clastogenicity

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Information Which Could Inform Future Toxicity Assessments

- Exposure dosimetric
  - Fiber concentration (current)
    - Surrogate measure of a subset of material
  - Lung burden – residence time
  - Surface area
  - Relative fiber potency
- Episodic versus cumulative exposure
  - Short-term high intensity, shorter latency?
  - Deposition / clearance modeling
  - Less-than lifetime risk

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Data gaps which may be informed by animal studies

- Proof of the principle
  (e.g. LA displays the same toxicity as other mineral fibers)
- Mode of action
  - Relative to other asbestos and mineral fibers
  - Can this inform low dose extrapolation
- Early lifetime susceptibility
- Episodic versus cumulative exposure
- Explore dosimetrics

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General Approach

- Tiered approach to studies
  - Relative dissolution *in vitro*
  - *in vitro* mechanisms (ROS, RNS etc.)
  - Short-term *in vivo*
  - Intermediate and chronic *in vivo*
- Use other forms of asbestos as controls
  - Tremolite (UICC)
  - Amosite
  - Chrysotile (?)
- Measured dose
  - Fiber count
  - Dimensional characteristics
  - Mass
  - Surface are (?)
- Tissue dose (initial and over time)
- Harmonize with noncancer studies

Caution regarding quantitative extrapolation from animal studies to human exposures